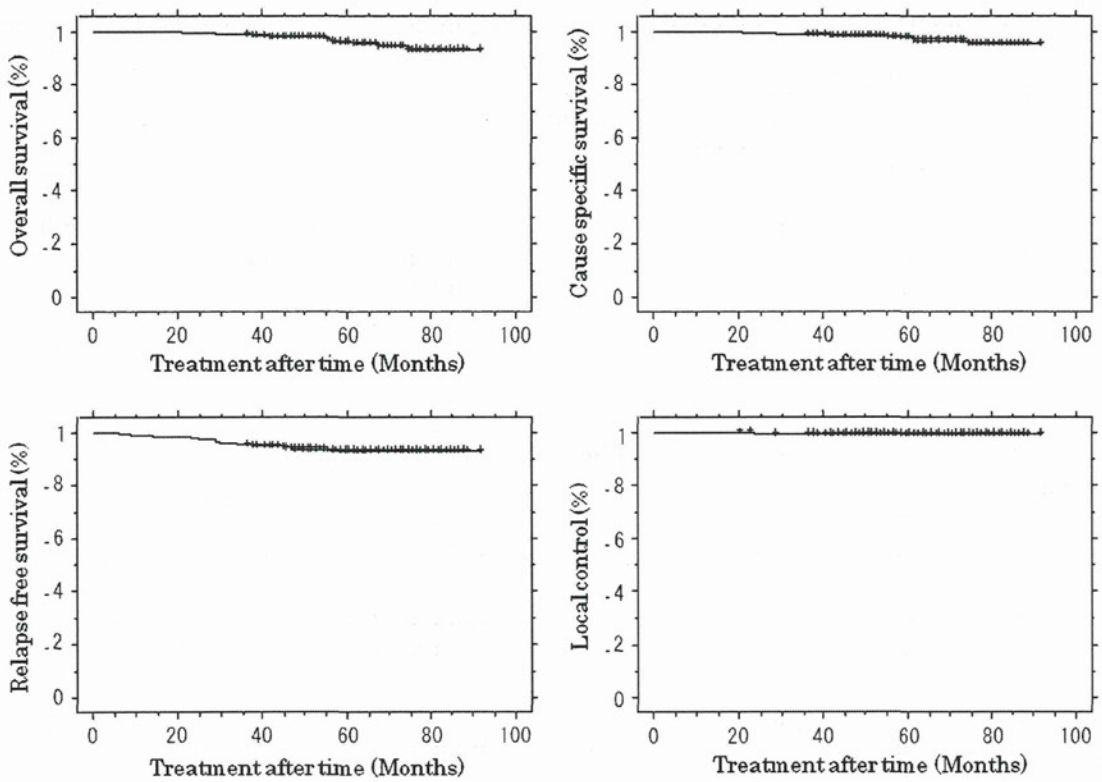

Fig. 2 Cause-specific survival of 327 patients at each pStage. The patients were divided by stage, as follows: stage 0, 29 patients; stage I, 164 patients; stage IIA, 107 patients; and stage IIB, 27 patients

5-year CSS for each stage. Actuarial 5-year CSS for each stage were: stage 0, 100%; stage I, 97.7%; stage IIA, 96.7%; and stage IIB, 96.3%.

Table 2 summarizes the relationship between RFS and other variables. Univariate analysis indicated that hormone therapy ($P = 0.0009$; HR 4.75; CI 1.72–13.10) was a significant prognostic factor for RFS. Multivariate analysis, using stepwise selection, similarly showed that hormone therapy ($P = 0.0027$; HR 4.71; CI 1.71–13.01) was a significant prognostic factor for RFS in this study.

Radiotherapy-induced dermatitis was observed for 268 patients (251 patients with grade 1, 17 with grade 2). Most patients did not need treatment for their dermatitis, but some were given appropriate drugs (e.g., an ointment or a steroid-containing cream). Two to six months after the completion of radiotherapy, 16 patients developed radiation pneumonitis (11 patients with grade 1, five with grade 2). No patients had radiation pneumonitis of grade 3 or higher. In addition, two patients were diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP). They received treatment with prednisolone and the symptoms improved. Concerning late toxicity, we observed no patients with grade 2 or higher toxicity.

Discussion

Hypofractionated radiotherapy to the whole breast after BCS is an alternative to radiotherapy with conventional fractionation. In Japan, however, there are no studies that report the long-term outcome of hypofractionated radiotherapy, and in fact, it is still less common. We previously reported preliminary results of the hypofractionated regimen [21]. At a median follow-up of 26 months, we obtained good results for OS, CSS, DFS, and LC. The objective of this study was to update our previous findings, after long-term observation.

Our current study shows acceptable results (with regard to OS, CSS, RFS, and LC); in Table 3 these are compared with those from other studies that used a hypofractionated or conventional regimen [14, 17, 22, 23]. The high LC is particularly notable. We believe there are two main reasons for this. First, all patients in this study received either Bp or Bq. Veronesi et al. [4, 24] reported that annual local recurrence was low for patients treated with Bq + radiotherapy (RT) whereas it was significantly higher for patients treated with Tm + RT. Another reason may be the definitions of "margin-free." In Japan, the definition of "stump-positive" is that cancer cells remain within 5 mm

Table 2 Characteristics of 327 breast cancer patients listed by the number of patients at risk, number of relapses, relapse-free survival, log rank test, Cox-regression, and specific hazard risk (HR)

Factor	No. of patients	No. of relapses	Relapse-free survival (5 years) (%)	*P*-value (log rank)	HR (CI 95%)†	*P* value (Cox-regression)	HR (CI 95%)††
Age							
<50	115	2	98.3		0.28 (0.06–1.24)		0.28 (0.06–1.25)
≥50	212	13	93.7	0.07	1.0 (reference)	0.09	1.0 (reference)
Bp or Bq	29	1	96.6		0.68 (0.08–5.67)		
+SNB	117	6	94.6		1.0 (reference)		
+Ax	181	8	95.5	0.92	0.85 (0.30–2.48)		
Chemotherapy							
Yes	109	7	93.5		1.0 (reference)		
No	218	8	96.2	0.26	0.56 (0.21–1.57)		
Hormone therapy							
Yes	261	7	97.3		1.0 (reference)		1.0 (reference)
No	66	8	87.4	0.0009	4.75 (1.72–13.10)	0.0027	4.71 (1.71–13.01)
PN stage							
0	261	11	95.7		0.69 (0.22–2.17)		
1	66	4	93.8	0.52	1.0 (reference)		
Margins							
Positive	66	5	92.3		1.0 (reference)		
Negative	261	10	96.0	0.18	0.49 (0.17–1.43)		
ER and/or PgR*							
Positive	253	11	95.5		1.0 (reference)		
Negative	38	4	89.5	0.09	2.59 (0.83–8.14)		
HER2*							
Positive	30	3	90.0		1.0 (reference)		
Negative	252	11	95.5	0.17	0.42 (0.11–1.51)		

For other abbreviations, see Table 1

* Some data are missing

† Univariate analysis

†† Multivariate analysis using Cox proportional hazard regression

Table 3 Comparison of our data with published data

Ref.	Patients	Operation type	RT dose/fraction	Overall survival	Local recurrence
Lyon [22]	1,024	Bp	50 Gy/25 fr	99% (4 years)	4.5% (4 years)
			50 Gy/25 fr + boost	99% (4 years)	3.5% (4 years)
EORTC [23]	5,318	Tm	50 Gy/25 fr	87% (5 years)	7.3% (5 years)
			50 Gy/25 fr + boost	91% (5 years)	4.3% (5 years)
OCOG trial [14]	622	Tm	42.56 Gy/16 fr	97.2% (5 years DFS)	3.4% (5 years)
START B trial [17]	1,110	BCS or Bt	40 Gy/15 fr ± boost	92% (5 years)	2.2% (5 years)
Our data	327	Bp or Bq	42.56 Gy/16 fr ± boost	96.0% (5 years)	0.3% (5 years)

Bt mastectomy; *fr* fraction; for other abbreviations, see Table 1

of the surgical margin; this is a more rigid criterion than that widely used in other countries. In our study, 66 patients had positive stumps and received additional boost irradiation. Several studies report that additional boost irradiation of the tumor bed after BCS reduced local recurrence irrespective of the stump status [4, 5, 7, 22, 23]. Therefore, the fact that many patients in our series received additional boost irradiation based on the rigid criterion may have resulted in good LC. Furthermore, our boosted dose of 13.3 Gy/5 fx seems relatively high, although the

appropriate dose of boost irradiation has not been established. These factors may be responsible for low local recurrence.

Radiation dermatitis and pneumonitis after breast-conserving therapy in our institution has been surveyed previously. Yoden et al. [25] reported the incidence of this toxicity for patients treated with conventional regimen and Fujii et al. [21] reported it for patients treated with hypofractionated regimen. They reported similar results, and the results from this study are compatible with these two reports. Irradiation of the breast using a hypofractionated schedule may cause more severe skin telangiectasia, fibrosis, or indurations, which worsens the final cosmetic outcome. Two randomized trials proved, by long-term observation, there was no difference in cosmetic outcomes between conventional and hypofractionated regimens [14, 15, 17]; our study also obtained satisfactory results for late toxicity. The follow-up period of this study may not be long enough to clarify late toxicity, because it is known that occurrence and grade of late toxicity increase in proportion to the time from completion of radiotherapy. Longer follow up is needed.

The purpose of this study was to prove the efficacy and safety of hypofractionated radiotherapy after BCS in Japanese women. In conclusion, we observed acceptable local control and survival without severe late toxicity after 5 years in our retrospective study. Although cosmetic outcomes must be clarified with longer follow up, we believe that this hypofractionated regimen can be used as practical clinical treatment. We believe that widespread of hypofractionated radiotherapy after BCS will help to reduce financial and temporal burdens on patients, and also help to accommodate the exponentially increasing number of cancer patients needing radiotherapy.

Conflict of interest None.

References

1. Malmstrom P, Holmberg L, Anderson H, Mattsson J, Jonsson PE, Tenvall-Nittby L, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node negative breast cancer: a randomized clinical trial in a population with access to public mammography screening. Eur J Cancer. 2003;39:1690–7.
2. Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol. 1999;17:2326–33.
3. Renton SC, Gazet JC, Ford HT, Corbishley C, Sutcliffe R. The importance of the resection margin in conservative surgery for breast cancer. Eur J Surg Oncol. 1996;22:17–22.
4. Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, del Vecchio M, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. Eur J Cancer. 1995;31A:1574–9.
5. Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. Lancet. 1996;348:708–13.
6. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233–41.
7. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst. 1996;88:1659–64.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favorable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. Lancet. 2000;355:1757–70.
9. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 2004;96:115–21.
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;366:2087–106.
11. Ash DV, Benson EA, Sainsbury JR, Round C. Seven-year follow-up on 334 patients treated by breast conserving surgery and short course radical postoperative radiotherapy: a report of the Yorkshire Breast Cancer Group. Clin Oncol. 1995;7:93–6.
12. Olivotto IA, Weir LM, Kim-Sing C, Bajdik CD, Trevisan CH, Doll CM, et al. Late cosmetic results of short-fractionation for breast conservation. Radiother Oncol. 1996;41:7–13.
13. Shelly W, Brundage M, Hayter C, Paszat L, Zhou S, Mackillop W. A shorter fractionation schedule for postlumpectomy breast cancer patients. Int J Radiat Oncol Biol Phys. 2000;47(5):1219–28.
14. Whelan T, MacKenzie R, Julian J, Levine M, Shelly W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143–50.
15. Whelan T, Pignol J, Levine M, Julian J, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513–20.
16. The START Trialists' Group. The U.K. Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet Oncol. 2008;9:331–41.
17. The START Trialists' Group. The U.K. Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet. 2008;371:1098–107.
18. Cox J, Stetz J, Pajak T. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341–6.
19. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer. 1977;35:1–39.
20. Cox DR. Regression models and life-tables. J R Stat Soc B. 1972;334:187–202.
21. Fujii O, Hiratsuka J, Nagase N, Tokiya R, Yoden E, Sonoo H, et al. Whole-breast radiotherapy with shorter fractionation schedules following breast-conserving surgery: short-term morbidity and preliminary outcomes. Breast Cancer. 2008;15:86–92.

22. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15(3):963–8.
23. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345(19):1378–87.
24. Veronesi U, Volterrani F, Luini A, Saccozzi R, Del Vecchio M, Zucali R, et al. Quadrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer. 1990;26(6):671–3.
25. Yoden E, Hiratsuka J, Imajyo Y. Radiation dermatitis and pneumonitis following breast conserving therapy. J Jpn Soc Ther Radiol Oncol. 2000;12:237–46 (in Japanese with English abstract).

Radiotherapy and Oncology 103 (2012) 25–31

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Proton RT in pancreatic cancer

A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis ☆

Kazuki Terashima [a,*], Yusuke Demizu [a], Naoki Hashimoto [a], Dongcun Jin [a], Masayuki Mima [a], Osamu Fujii [a], Yasue Niwa [a], Kento Takatori [b], Naoto Kitajima [b], Sachiyo Sirakawa [c], Ku Yonson [c], Yoshio Hishikawa [a], Mitsuyuki Abe [a], Ryohei Sasaki [d], Kazuro Sugimura [e], Masao Murakami [a]

[a] Department of Radiology, Hyogo Ion Beam Medical Center; [b] Department of Internal Medicine, Kasai City Hospital; [c] Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine; [d] Division of Radiation Oncology, Kobe University Graduate School of Medicine; [e] Division of Radiology, Kobe University Graduate School of Medicine, Hyogo, Japan

ARTICLE INFO

Article history:
Received 20 August 2011
Received in revised form 15 December 2011
Accepted 20 December 2011
Available online 31 January 2012

Keywords:
Proton radiotherapy
Gemcitabine
Pancreatic cancer
Locally advanced
Chemoradiotherapy

ABSTRACT

Purpose: We conducted the study to assess the feasibility and efficacy of gemcitabine-concurrent proton radiotherapy (GPT) for locally advanced pancreatic cancer (LAPC).
Materials and methods: Of all 50 patients who participated in the study, 5 patients with gastrointestinal (GI)-adjacent LAPC were enrolled in P-1 (50 Gy equivalent [GyE] in 25 fractions) and 5 patients with non-GI-adjacent LAPC in P-2 (70.2 GyE in 26 fractions), and 40 patients with LAPC regardless of GI-adjacency in P-3 (67.5 GyE in 25 fractions using the field-within-a-field technique). In every protocol, gemcitabine (800 mg/m^2/week for 3 weeks) was administered concurrently. Every patient received adjuvant chemotherapy including gemcitabine after GPT within the tolerable limit.
Results: The median follow-up period was 12.5 months. The scheduled GPT was feasible for all except 6 patients (12%) due to acute hematologic or GI toxicities. Grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10%) in P-2 and P-3. The one-year freedom from local-progression, progression-free, and overall survival rates were 81.7%, 64.3%, and 76.8%, respectively.
Conclusion: GPT was feasible and showed high efficacy. Although the number of patients and the follow-up periods are insufficient, the clinical results seem very encouraging.
 Radiotherapy and Oncology 103 (2012) 25–31

The prognosis of pancreatic cancer is poor, with a five-year survival rate of about 5% in total [2]. Only radical surgical resection has been shown to cure the condition, although the five-year survival rate remains low at about 10–20%. And only 15–20% of all patients with pancreatic cancer can be treated by resection, while the other patients cannot undergo resection because of local invasion or distant metastasis at diagnosis [4,9].

For the treatment of non-resectable pancreatic cancers, chemoradiotherapy (CRT) with concurrent 5-fluorouracil (5-FU) is historically considered the standard therapy for locally advanced pancreatic cancer (LAPC) [6,18,26]. Recently, based on a background of favorable results of gemcitabine-based chemotherapy [1,9], and the fact that gemcitabine is a potent radio-sensitizer [16], many studies on gemcitabine-concurrent CRT have been performed for LAPC [7,17,20,24], and indicate the possibility of an improvement in survival. These studies have shown that reduction of the irradiation doses and target fields was necessary when gemcitabine was administered at or near the full dose (1000 mg/m^2). In contrast, a reduction of the gemcitabine dose was needed when irradiation was administered at doses over 50 Gy, which is necessary for the local control of malignant tumors. The reason for these restrictions of the chemoradiotherapy was speculation that the region of gastrointestinal (GI) tract located near the pancreas was irradiated beyond tolerable doses. Consequently, we thought that proton beam radiotherapy could deliver higher dose above 50 Gy concurrently with a higher dose of gemcitabine to a larger field containing the draining and paraaortic lymph nodes and peripheral regions surrounding the celiac artery and superior mesenteric artery.

Radiotherapy using protons or carbon-ions is currently attracting worldwide interest because of its physical properties including superior dose distribution to a target, which allows selective irradiation to the tumor, while minimizing irradiation of the surrounding normal tissues [10,15,25]. In our pilot study, proton beam radiotherapy alone was performed at doses of 40 and 50 GyE for patients with LAPC between November 2004 and October 2006 [12]. Although local control and survival did not reach significance in

☆ This study has not been presented previously.

* Corresponding author. Address: Department of Radiology, Hyogo Ion Beam Medical Center, 1-2-1 Kouto, Shingu-cho, Tatsuno, Hyogo 679-5165, Japan.
E-mail address: terashima@kmyr.jp (K. Terashima).

0167-8140/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2011.12.029

comparison with other treatments, such as chemotherapy alone or CRT, we confirmed the feasibility and safety of proton radiotherapy. Based on this pilot study, we started gemcitabine-concurrent proton radiotherapy (GPT) for LAPC to assess the feasibility and efficacy of this regimen. To our knowledge, this is the first report on the clinical use of concurrent gemcitabine and proton radiotherapy for the treatment of pancreatic cancer.

Patients and methods

Patient eligibility

Patients with LAPC which was defined as borderline resectable cancer and unresectable cancer without distant metastases [28], that was cytologically or histologically confirmed to be adenocarcinoma, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and were in adequate physical condition to tolerate chemotherapy were eligible for this study. Patients with a history of abdominal radiotherapy or previous treatment of pancreatic tumor were excluded.

All patients provided written informed consent prior to enrollment. The study was approved by the institutional review board and registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, http://www.umin.ac.jp/ctr, UMIN ID: UMIN000002173).

Pretreatment workup

At baseline, all patients underwent an abdominal contrast-enhanced computed tomography (CT) scan, chest CT scan, positron emission tomography with ^{18}F-fluorodeoxy glucose (FDG-PET), and gastrointestinal fiberscopy (GIF) and were assessed for tumor markers (CA19-9, CEA, DUPAN-2, and SPAN-1). The disease was staged according to the International Union Against Cancer (UICC) TNM staging system, 6th edition.

Treatment regimen

Concurrent and adjuvant chemotherapy

In all protocols, all patients were scheduled to receive intra-venous infusion of gemcitabine (800 mg/m^2) for 30 min for the initial 3 weeks (days 1, 8, and 15) during 5 weeks of proton radiotherapy. We determined the dose of gemcitabine according to the studies by Casper et al. [3] and Burris et al. [1], and the schedule according to the study by Murphy et al. [20]. Gemcitabine was administered if the absolute granulocyte count was >2000/mm^3 and the platelet count was >70000/m^3 on the scheduled day.

Following GPT, all patients received systemic gemcitabine-based chemotherapy for as long as possible.

Proton radiotherapy

Hyogo Ion Beam Medical Center (HIBMC) treats patients with both proton and carbon-ion beams. We decided to use proton therapy for this study, because proton beams can be delivered to the target from any direction by using a rotating gantry so that irradiation of the GI tract is minimized. However, a rotating gantry is not available for carbon ion therapy. Furthermore, we anticipated that the administration of gemcitabine would have a sensitizing effect on proton therapy, as previously shown in human pancreatic cancer cells [5].

The patients were treated with 150–210 MeV proton beams. A respiratory gating system was used for all patients to irradiate the beam during the exhalation phase. Patient set-up was performed daily by subtraction of the 2 sets of orthogonal digital radiographs before irradiation. The translation and rotation of the patient detected by the positioning system were compensated for by adjustment of the treatment couch. The setup was continued until the bony landmarks on the digitally reconstructed radiographs agreed within 1 mm. The biologic effects of proton therapy at our institution were evaluated in vitro and in vivo. The relative biologic effectiveness (RBE) values were determined to be 1.1 by biologic experiments [11]. Because all tissues are assumed to have almost the same RBE, doses expressed in GyE are directly comparable to photon doses.

Treatment planning

Proton beam treatment plans were developed using a CT-based 3-dimensional treatment planning system. The gross tumor volume (GTV) was defined as the primary tumor plus the apparent lymph nodes as determined by a fusion contrast-enhanced CT subsidiary using FDG-PET. The clinical target volume (CTV) comprised the addition of a 5-mm margin to the GTV and prophylactic irradiation regions containing the draining lymph nodes and paraaortic lymph nodes as well as peripheral regions surrounding the celiac artery and superior mesenteric artery. We defined the CTV to contain the prophylactic region because metastases to regional lymph nodes have been recognized as prognostic factors in some studies of CRT [8] and resection [23,27] for LAPC. The planning target volume (PTV) was defined as the CTV plus a setup margin (5 mm) and a respiratory gating margin (1–5 mm), which was measured on CT images between inspiratory and expiratory phases. In general, the stomach, small bowel including the duodenum, kidneys, and spinal cord were defined as organs-at-risk (OAR). The dose restrictions for stomach, duodenum, and spinal cord were approximately 50 GyE, 50 GyE, and 45 GyE, respectively [13,14]. Additionally, we planned the irradiated volumes of the stomach, duodenum, and kidneys to be as small as possible.

Dose-fractionation

A total of 3 protocols were used in this study. In the early phase of the study, 2 protocols were used contemporaneously; protocol P-1 (50 GyE in 25 fractions) was used for patients with GI-adjacent LAPC, and P-2 (70.2 GyE in 26 fractions) was used for those with non-GI-adjacent LAPC. The non-GI-adjacent LAPC were defined as tumors that could be treated with irradiation plans that covered the GTV: over 95% of the prescribed dose in P-2 (70.2 GyE), which kept the dose administered to the GI-tract under 50 GyE. The others were defined as GI-adjacent LAPC who were treated with P-1. After the early phase, all patients were treated with protocol P-3 (67.5 GyE in 25 fractions) using the field-within-a-field technique.

In P-1, a total dose of 50 GyE was delivered in 25 fractions over 5 weeks to the PTV, based on our pilot study [12] and the report of 5-FU-concurrent CRT [19], in which irradiation doses of 39.6–50.4 Gy did not result in any late GI toxicity. In P-2, 70.2 GyE in 26 fractions over 6 weeks was delivered to the PTV. This approach was designed based on our experiences in treating head and neck cancers and lung cancer as well as other tumors, in which 70.2 GyE in 26 fractions was employed after dose escalation from 65 GyE in 26 fractions [21].

In P-3, 67.5 GyE in 25 fractions over 5 weeks was delivered using the field-within-a-field technique. With this technique, we used three types of split doses: 2 + 0.7 GyE, 1.8 + 0.9 GyE, and 1.6 + 1.1 GyE. For example, we delivered 1.8 GyE to the whole PTV (Fig. 1a) and 0.9 GyE to the PTV excluding the GI tract including stomach, small bowel, and large bowel, in one fraction (Fig. 1b). Consequently, a maximum dose of 2.7 GyE was administered as a single fraction (total 67.5 GyE) to the majority of the PTV (Fig. 1c), in parallel with limiting the dose to the GI tract to approximately

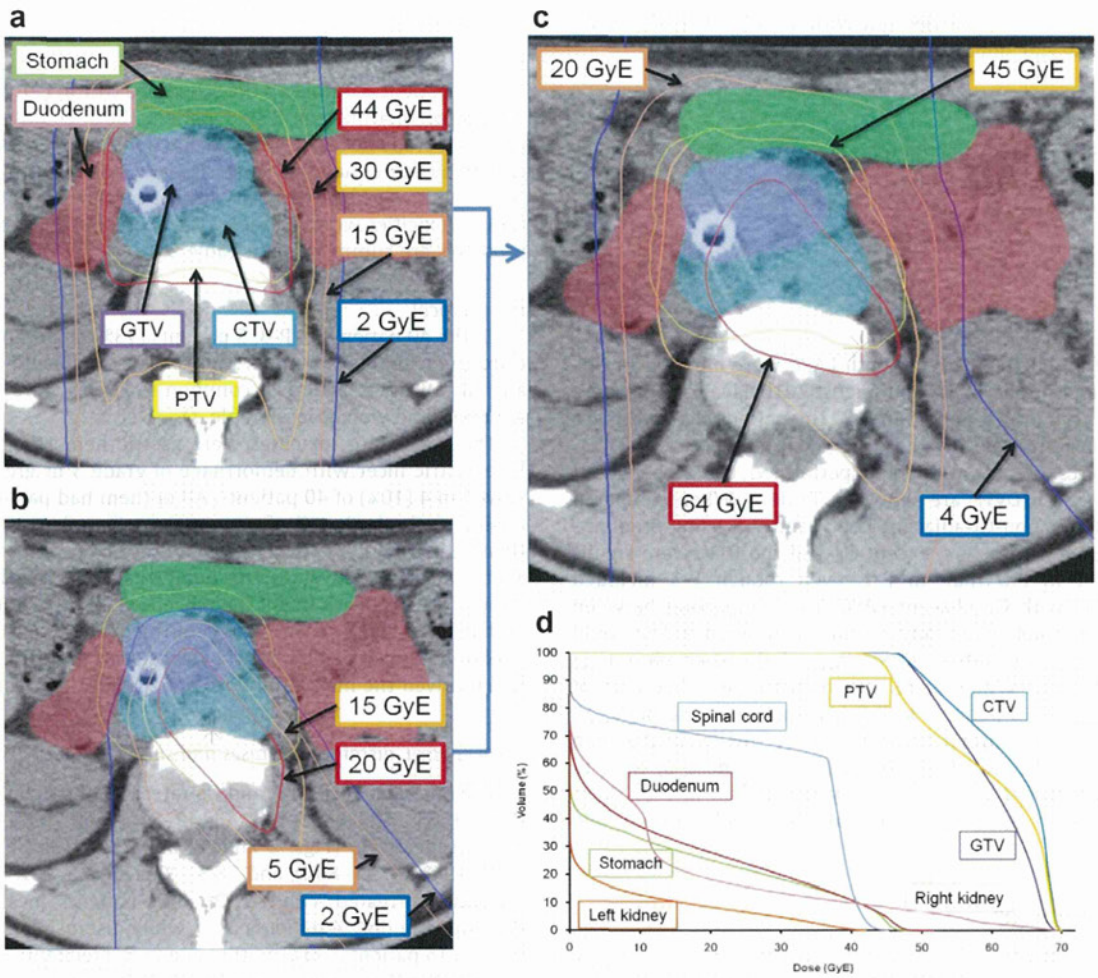

Fig. 1. A representative patient with locally advanced pancreatic cancer that was adjacent to the GI tract, treated with the gemcitabine-concurrent proton therapy (GPT) under protocol-3 (using the field-within a-field technique). (a) Dose distribution of the proton beam only at 1.8 GyE per fraction. A total dose of 45 GyE, which was the minimal dose administered to the PTV, was administered to the entire PTV. (b) Dose distribution at 0.9 GyE per fraction. A total dose of 22.5 GyE was irradiated to the PTV except for the GI tract (stomach and duodenum). (c) Summation of 1.8 GyE and 0.9 GyE in daily fractions. A total dose of 67.5 GyE was administered as the maximum dose, while the stomach and duodenum were only irradiated with approximately 45 GyE. (d) The dose–volume histogram of this plan for gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and the organs-at-risk (stomach, duodenum, bilateral kidneys, and spinal cord).

1.8 GyE (total 45 GyE). With this technique, it became possible to treat all patients with the P-3 protocol alone, independent of GI-adjacency.

Follow-up

All patients received abdominal contrast-enhanced CT every three months and tumor marker monitoring every month after GPT. GIF was performed at the end of the GPT and every three-months thereafter to evaluate GI toxicity. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Comparison of the protocols

To clarify the characteristics and effectiveness of the field-within-a-field technique, we analyzed the treatment plans for proton therapy using a dose-volume histogram (DVH) and compared P-3 with P-1 and P-2 in terms of $D_{80\%}$, $D_{50\%}$, and $D_{20\%}$ ($D_{x\%}$ indicates the dose delivered to $x\%$ of the target volume) of the GTV, CTV, and PTV, as well as D_{max} (a maximum dose to the target) of the stomach and duodenum.

Evaluation of local control

As the radiographic changes caused by the GPT were not significant, local control was judged comprehensively by changes in the maximum tumor diameter, the inner density on contrast-enhanced CT, the levels of tumor markers including CA19-9 and CEA, which are particularly useful for pancreatic cancer [29], and the accumulation on FDG-PET. We conclusively defined local progression as radiographic enlargement of the primary tumor or locoregional recurrence or tendency to increase in tumor markers for at least three months without any distant metastases.

End points and statistical analysis

The primary end points were feasibility and toxicity, and the secondary end points were freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS). These were estimated from the date of the GPT initiation to the date of the event or the last follow-up.

The FFLP, PFS, and OS rates were calculated using the Kaplan–Meier method. Unpaired Student's *t*-test was used to compare parameters of dose–volume histograms between the protocols.

Statistical analyses were carried out with SPSS Version 17.0 software (SPSS, Chicago, Illinois, USA).

Role of funding source

The sponsors of the study did not play any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient and tumor characteristics

A total of 50 eligible patients with LAPC were enrolled in this study between February 2009 and August 2010. Five patients were enrolled in P-1, 5 in P-2, and 40 in P-3. The patient characteristics are summarized in Table 1.

The analyses of proton therapy performed using the dose–volume histogram (DVH) are shown in Table 2. When compared between P-1 (for non-GI-adjacent LAPC) and P-3 using Student's *t*-test, all of the parameters, except $D_{80\%}$ of the PTV, were significantly higher in P-3 than in P-1, even though P-3 included many patients with GI-adjacent LAPC. The comparison between P-2 and P-3 did not detect any significant difference. We could not find a significant difference for D_{max} of the stomach among P-1, P-2, and P-3. While there was a possibility that bias of tumor location (all 5 patients in P-2 had tumors in the body/tail of the pancreas) and tumor size (apparently smaller in P-2 than P-3) affected to the statistical result, the mean dose of D_{max} to the duodenum in P-3 was significantly lower than in P-2. These findings support the superiority of the field-within-a-field technique.

Adjuvant chemotherapy

Among 50 patients, 45 patients (90%) were able to continue adjuvant systemic gemcitabine-based chemotherapy after GPT. Five patients (10%) failed because of unacceptable toxicity of the adjuvant chemotherapy or rapid disease progression.

Feasibility and toxicity

P-1 and P-2 protocols

All 5 patients completed the scheduled GPT in P-1. Four patients completed treatment in P-2; 1 patient (20%) could not complete proton therapy at 62.1 GyE in 23 fractions due to gastric bleeding caused by acute radiation mucositis and was cured by medication only. There was no late toxicity in that case. In P-1 and P-2, hematologic toxicities were tolerable. The acute and late toxicities in all protocols are summarized in Table 3.

P-3 protocol

Of the 40 patients in P-3, 5 patients (13%) could not receive the third gemcitabine administration because of acute hematologic and GI toxicities. The most common toxicities were neutropenia, anorexia, and weight loss (Table 3).

The major late toxicities were gastric hemorrhage and ulcer. Late gastric ulcer with hemorrhage of grade 3 or greater was observed in 4 (10%) of 40 patients. All of them had pancreatic cancer arising in the body/tail of pancreatic region. Among these 4 patients, 3 patients (8%) were cured with medication (grade 3), but 1 patient (3%) died of gastric hemorrhage six months after GPT (grade 5). This death might have been related to the GPT because gastric ulcer and erosion were confirmed by GIF on the posterior wall of the lower gastric body 2 weeks prior to death. This patient had received the maximum dose of 52 GyE to the stomach.

Local control, distant metastases and survival

The one-year FFLP, PFS, and OS rates for all patients were 81.7% (95% CI: 65–99%), 64.3% (95% CI: 48–81%), and 76.8% (95% CI: 64–89%), respectively (Figs. 2 and 3), and 79.9% (95% CI: 58–100%), 60.8% (95% CI: 41–80%), and 78.8% (95% CI: 65–93%), respectively for patients treated with P-3. Of all 50 patients, local progression developed in only 4 patients (8%), while distant metastasis developed in 15 patients (30%), within one year. Frequent sites of distant metastasis were the liver in 9 patients (18%), lung in 1 patient (2%), and the peritoneum in 3 patients (6%). Five patients (10%) were already diagnosed with liver metastases at the end of GPT. None of

Table 1
Patient characteristics.

Characteristic	Protocol P-1 ($n = 5$)	Protocol P-2 ($n = 5$)	Protocol P-3 ($n = 40$)
Follow-up time, months			
Median (range)	12.3 (8.2–18.6)	19.6 (17.7–21.5)	12.1 (3.2–22.3)
Age, years			
Median (range)	57 (55–75)	56 (45–72)	64 (49–83)
Gender			
Male	3	2	18
Female	2	3	22
ECOG-PS			
0	2	3	27
1	3	2	10
2	0	0	3
UICC-TNM			
T3N1M0	0	1	4
T4N0M0	1	2	6
T4N1M0	4	2	30
Tumor location			
Head	1	0	18
Body/tail	4	5	22
Tumor size, cm			
Median (range)	4.6 (3.1–5.6)	3.2 (4.5–7.2)	3.7 (2.5–7)
CEA, ng/mL			
Median (range)	3.8 (1–12)	1.6 (1–6)	3 (0.9–16.4)
CA19–9, U/mL			
Median (range)	999 (0–6010)	73.2 (15–731)	185 (0–27600)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; UICC-TNM, the International Union Against Cancer (UICC) TNM staging system.

Table 2
Summary of proton therapy.

	P-1 50 GyE/25 fr Median (range), GyE	P-2 70.2 GyE/26 fr Median (range), GyE	P-3 67.5 GyE/25 fr Median (range), GyE	*t*-test (P-1, P-3) *P*-value	*t*-test (P-2, P-3) *P*-value
GTV $D_{80\%}$	49.9 (49.6–50)	58.2 (43.6–68.1)	53.4 (43.1–66.4)	<0.01	0.12
GTV $D_{50\%}$	50.2 (50–50.4)	64.4 (49.2–70.1)	61.1 (50.2–67.6)	<0.01	0.22
GTV $D_{20\%}$	50.6 (50.4–50.8)	66.6 (52.3–70.4)	66 (57.1–68.1)	<0.01	0.88
CTV $D_{80\%}$	49.9 (49.4–50.4)	56.1 (41.9–65.6)	52.5 (41.7–60)	<0.01	0.19
CTV $D_{50\%}$	50.3 (50–50.5)	64.4 (48.9–69.1)	62.6 (53.2–67.1)	<0.01	0.68
CTV $D_{20\%}$	50.7 (50.5–51)	66.6 (51.6–70.8)	67.4 (65.4–68.2)	<0.01	0.85
PTV $D_{80\%}$	49.7 (49.4–50.1)	51.6 (36.6–60.7)	49.4 (40.8–61)	0.72	0.42
PTV $D_{50\%}$	50.3 (50–50.5)	61.4 (46.2–67.6)	59.5 (46.3–66.5)	<0.01	0.50
PTV $D_{20\%}$	50.8 (50.6–51.2)	66.3 (50.8–70.4)	66.9 (63.1–68)	<0.01	0.89
Stomach D_{max}	51 (4–52)	46 (39–56)	48 (38–52)	0.52	0.54
Duodenum D_{max}	41 (40–46)	51 (51–52)	48.5 (42–52)	<0.01	<0.01

Abbreviations: GyE, gray equivalents; fr, fractions; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; $D_{x\%}$, dose delivered to $x\%$ of the target volume; D_{max}, maximum dose.

Table 3
Acute and late adverse events of grade 3 or greater.

Toxicity	P-1 ($n = 5$)		P-2 ($n = 5$)				P-3 ($n = 40$)							
	Acute		Acute		Late		Acute				Late			
	Grade 3		Grade 3		Grade3		Grade 3		Grade 4		Grade 3		Grade 5	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Hematologic														
Leukopenia	1	(20)	3	(60)			15	(38)	1					
Neutropenia	1	(20)	2	(40)			9	(23)	2					
Anemia			1	(20)										
Thrombocytopenia			1	(20)			2	(5)						
Gastrointestinal														
Nausea							2	(5)						
Vomiting							1	(3)						
Anorexia	1	(20)	1	(20)			3	(8)			1	(3)		
Epigastralgia	1	(20)					2	(5)						
Gastric ulcer					1	(20)					3	(8)	1	(3)
Miscellaneous														
Weight loss							3	(5)						
Fatigue	1	(20)					1	(3)			1	(3)		

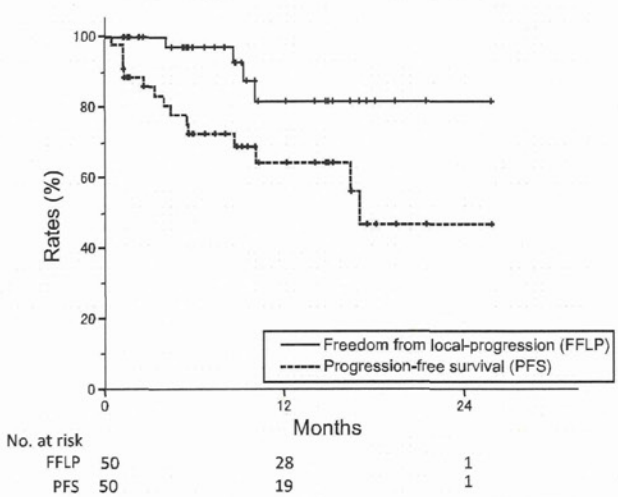

Fig. 2. The freedom from local-progression (solid line) and progression-free (dashed line) survival rates for all patients.

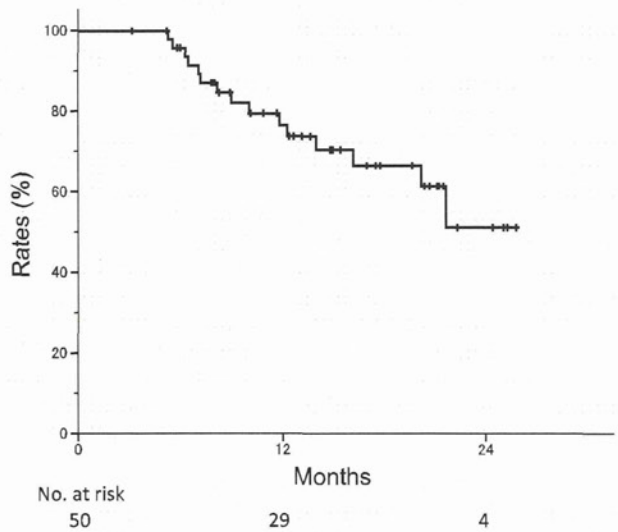

Fig. 3. The overall survival rate for all patients.

the patients died of local progression. One patient (2%) who developed both locoregional and distant metastases died of gastric hemorrhage (grade 5). Twelve patients (24%) have survived over 12 months to date without any signs of local or distant tumor progression.

Discussion

Our study indicated the high feasibility and tolerability of proton radiotherapy concurrently with high dose gemcitabine at 800 mg/m^2 on days 1, 8, and 15 during proton beam radiotherapy. The low frequency of grade 3 or greater acute GI toxicities, even at doses as high as 70.2 GyE (P-2) or 67.5 GyE (P-3), suggests superior dose localization of the proton beams to the target. However, late GI toxicities in P-3 (gastric ulcer and hemorrhage of grade 5) cannot be disregarded. We recognized that gastric peristalsis might bring unexpected high dose to the stomach, leading to severe complications in those patients, but it is a limitation of the current treatment planning technique. To prevent these major late toxicities, we have restricted irradiation doses to the GI tract by regulating the target fields and gantry angles and selecting an optimal split dose for the field-within-a-field technique. In contrast to the gastric toxicities, we did not encounter critical ulcer or hemorrhage in the duodenum, although it was irradiated at a dose similar to that of the stomach. The reason that no serious GI toxicity occurred in patients with pancreatic body/tail cancer seems to stem from the tolerability of the duodenum. As this lower frequency of duodenal toxicity is very interesting, we continued careful observation of the duodenum by duodenal fiberscopy.

From our clinical experience, it appears that the field-within-a-field technique that we used at P-3 enabled us to reduce the irradiation of OAR while maintaining the necessary doses to the PTV. Our analyses of the DVH indicate that using the field-within-a-field technique can increase the dose to the PTV of patients with GI-adjacent LAPC. Despite an increase in the dose to the PTV, the maximum dose to the stomach and duodenum was not increased. In addition, the optimal split dose of the field-within-a-field technique can be selected according to the tumor adjacency to the GI tract, so that the OAR are irradiated within a tolerable limit. Accordingly, GPT performed using the field-within-a-field technique contributed to solving of the mentioned three problems: reduction of irradiation dose, gemcitabine dose, and irradiation field.

Murphy et al. demonstrated that FFLP was a significant factor of OS on multivariate analysis [20]. To improve FFLP, our GPT was designed to deliver proton beams at a higher dose to a large CTV with concurrent administration of gemcitabine. As a result, the one-year FFLP and OS rates in our study were greater than expected, with high rates of 81.7% and 76.8%, respectively. This high FFLP rate is considered to be due to a large CTV, which was locally irradiated by proton beams at a high dose; thus, a good OS rate was achieved with low toxicities. However the one-year PFS rate was 64.3% which is low compared with the high FFLP and OS rates, this PFS rate is apparently better than that of other treatment modalities for patients with LAPC. Namely, the reported PFS rates are approximately 10–20% for CRT [7,17,22] and 10–15% for gemcitabine-based chemotherapy alone [1,9]. It is likely that the substantial local control of the primary tumor exerted by GPT decreased distant metastases and that the use of concurrent and adjuvant gemcitabine has contributed to the prolongation of life of patients with LAPC.

The one-year OS rate obtained in our study is apparently better than that obtained for patients treated with chemo-photon therapy [7,17,20]. Therefore, we consider that proton therapy using the field-within-a-field technique combined with concurrent gemcitabine or another promising chemotherapy has the potential to improve survival, including radical cure, for patients with LAPC.

Conclusions

GPT for LAPC was feasible and tolerable, and GPT using the field-within-a-field technique resulted in high FFLP and OS rates in our study. Although the number of patients enrolled in this study is too small and the follow-up periods are too short to draw any definitive conclusions, the clinical results obtained to date seem very encouraging.

Conflicts of interest

None.

References

[1] Burris 3rd HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–13.
[2] Carpelan-Holmstrom M, Nordling S, Pukkala E, et al. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. Gut 2005;54:385–7.
[3] Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994;12:29–34.
[4] D'Souza MA, Shrikhande SV. Pancreatic resectional surgery: an evidence-based perspective. J Cancer Res Ther 2008;4:77–83.
[5] Galloway NR, Aspe JR, Sellers C, Wall NR. Enhanced antitumor effect of combined gemcitabine and proton radiation in the treatment of pancreatic cancer. Pancreas 2009;38:782–90.
[6] GITSG. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst 1988;80:751–5.
[7] Huang PI, Chao Y, Li CP, et al. Efficacy and factors affecting outcome of gemcitabine concurrent chemoradiotherapy in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2009;73:159–65.
[8] Ikeda M, Okada S, Tokuuye K, Ueno H, Okusaka T. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. Cancer 2001;91:490–5.
[9] Ishii H, Furuse J, Boku N, et al. Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG0506. Jpn J Clin Oncol 2010;40:573–9.
[10] Iwata H, Murakami M, Demizu Y, et al. High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. Cancer 2010;116:2476–85.
[11] Kagawa K, Murakami M, Hishikawa Y, et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center. Int J Radiat Oncol Biol Phys 2002;54:928–38.
[12] Kamigaki T, Murakami M, Matsumoto IMM. A phase I study of proton beam therapy for locally advanced pancreatic cancer: analysis of feasibility and anti-tumor effect. J Clin Oncol 2008;26 [May 20 Suppl.; abstr 15675) 2008].
[13] Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose–volume effects in the stomach and small bowel. Int J Radiat Oncol Biol Phys 2010;76:S101–7.
[14] Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose–volume effects in the spinal cord. Int J Radiat Oncol Biol Phys 2010;76:S42–9.
[15] Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. Cancer 2011.
[16] Lawrence TS, Eisbruch A, McGinn CJ, Fields MT, Shewach DS. Radiosensitization by gemcitabine. Oncology (Williston Park) 1999;13:55–60.
[17] Li CP, Chao Y, Chi KH, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003;57:98–104.
[18] Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705–10.
[19] Morganti AG, Valentini V, Macchia G, et al. 5-Fluorouracil-based chemoradiation in unresectable pancreatic carcinoma: phase I–II dose-escalation study. Int J Radiat Oncol Biol Phys 2004;59:1454–60.
[20] Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2007;68:801–8.
[21] Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. Int J Radiat Oncol Biol Phys 2007;68:758–62.
[22] Okusaka T, Ito Y, Ueno H, et al. Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. Br J Cancer 2004;91:673–7.

[23] Ozaki H, Hiraoka T, Mizumoto R, et al. The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection. Surg Today 1999;29:16–22.
[24] Loehrer PJ, Powell ME, Cardenes HR, Wagner L, Brell JM, Ramanathan RK, et al. Eastern Cooperative Oncology Group. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. J Clin Oncol 2008;26 [May 20 Suppl.; abstr 4506].
[25] Schulz.-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 2007;25:953–64.
[26] Shinchi H, Takao S, Noma H, et al. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2002;53:146–50.
[27] Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–79.
[28] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011;378:607–20.
[29] Wong D, Ko AH, Hwang J, Venook AP, Bergsland EK, Tempero MA. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. Pancreas 2008;37:269–74.

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 4, pp. 1509–1514, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.04.052

CLINICAL INVESTIGATION **Head and Neck Cancer**

LONG-TERM OUTCOME AND PATTERNS OF FAILURE IN PRIMARY OCULAR ADNEXAL MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA TREATED WITH RADIOTHERAPY

NAOKI HASHIMOTO, M.D.,* RYOHEI SASAKI, M.D.,* HIDEKI NISHIMURA, M.D.,* KENJI YOSHIDA, M.D.,* DAISUKE MIYAWAKI, M.D.,* MASAO NAKAYAMA, M.S.,* KAZUYUKI UEHARA, M.S.,* YOSHIAKI OKAMOTO, M.D.,* YASUO EJIMA, M.D.,* ATSUSHI AZUMI, M.D.,† TOSHIMITSU MATSUI, M.D.,‡ AND KAZURO SUGIMURA, M.D.*

Divisions of *Radiation Oncology, †Ophthalmology, and ‡Hematology, Kobe University Graduate School of Medicine, Hyogo, Japan

Purpose: To evaluate the long-term treatment outcome and disease behavior of primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma (POAML) after treatment with radiotherapy.

Methods and Materials: Seventy-eight patients (42 male, 36 female) diagnosed with stage I POAML between 1991 and 2010 at Kobe University Hospital were included. The median age was 60 years (range, 22–85 years). The median radiation dose administered was 30.6 Gy. Rituximab-based targeted therapy and/or chemotherapy was performed in 20 patients (25.6%). Local control (LC), recurrence-free survival (RFS), and overall survival (OS) rates were calculated using the Kaplan-Meier method.

Results: The median follow-up duration was 66 months. Major tumor sites were conjunctiva in 37 patients (47.4%), orbita in 29 (37.2%), and lacrimal glands in 12 (15.4%). The 5- and 10-year OS rates were 98.1% and 95.3%, respectively. The 5- and 10-year LC rates were both 100%, and the 5- and 10-year RFS rates were 88.5% and 75.9%, respectively. Patients treated with a combination of radiotherapy and targeted therapy and/or chemotherapy had a trend for a better RFS compared with those treated with radiotherapy alone (p = 0.114). None developed greater than Grade 2 acute morbidity. There were 14 patients who experienced Grade 2 morbidities (cataract: 14; retinal disorders: 7; dry eye: 3), 23 patients who had Grade 3 morbidities (cataract: 23; dry eye: 1), and 1 patient who had Grade 4 glaucoma.

Conclusions: Radiotherapy for POAML was shown to be highly effective and safe for LC and OS on the basis of long-term observation. The absence of systemic relapse in patients with combined-modality treatment suggests that lower doses of radiation combined with targeted therapy may be worth further study. © **2012 Elsevier Inc.**

MALT lymphoma, Ocular adnexal lymphoma, Radiotherapy, Pattern of failure.

INTRODUCTION

Since the first description by Isaacson and Wright in 1983, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma has been recognized as a distinct entity of low-grade B-cell lymphoma; it is described in the revised European-American lymphoma (REAL) classification and also in the more-recent classification by the World Health Organization (WHO) (1–3). Malignant lymphoma arising in the ocular adnexa is a rare disorder, and previous reports have indicated that these lymphomas account for approximately 8% of all extranodal lymphomas (4). Several reports have indicated that the majority of lymphomas in the ocular adnexa are of MALT type (5–9). It was reported that histology, according to the REAL or WHO classification, could be used to accurately predict the prognosis of patients with lymphomas in the ocular adnexa and that patients with MALT-type lymphomas have a more favorable prognosis than those with lymphomas of different histology (6–9).

Mucosa-associated lymphoid tissue lymphomas have generally been believed to follow a relatively indolent course and show a tendency to remain localized within their original environment for a long period (10, 11). First-line treatment options include radiotherapy (standard), chemotherapy, or

Reprint requests to: Ryohei Sasaki, M.D., Ph.D., Kobe University Graduate School of Medicine, Division of Radiation Oncology, 7-5-2 Kusunokicho, Chuouku, Kobe City, Hyogo 650-0017, Japan. Tel: (+81) 78-3826104; Fax: (+81) 78-3826129; E-mail: rsasaki@med.kobe-u.ac.jp

Supported by Grants-in-Aid and Grants 21249066, 21591609, and 22591384 for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Y. Okamoto's present address: Department of Radiation Oncology, Osaka Police Hospital, Tennoji, Japan.

Y. Ejima's present address: Department of Radiology, Dokkyo Medical University, Tochigi, Japan.

Conflict of interest: none.

Received Feb 9, 2011, and in revised form April 14, 2011. Accepted for publication April 19, 2011.

even a wait-and-see policy in certain clearly defined patients (12). Therefore, there has been no consensus regarding the initial management of POAML to date; radiotherapy has been generally considered the most effective treatment for localized disease (13–19). Although results for local control (LC) by radiotherapy were satisfying, disease progression occurred in a fraction of patients. There have been few analyses of disease progression and death in patients with POAML (19–22).

After reporting our treatment outcomes for POAML treated with radiotherapy alone (23), we have started another protocol of radiotherapy combined with rituximab-based targeted therapy and/or chemotherapy. Several investigators demonstrated that although high LC was achieved by the radiotherapy for POAML, patterns of systemic relapse have not been elucidated (13, 18, 24, 25). The purposes of this analysis were to determine the long-term follow-up results of POAML patients treated with radiotherapy at our institution, to analyze patterns of failure of POAML, and to evaluate the outcome of patients treated with the radiotherapy combined with targeted therapy.

METHODS AND MATERIALS

Patients

Seventy-eight consecutive patients with histologically proven stage I ocular adnexal MALT lymphoma treated with radiotherapy at Kobe University Hospital between March 1991 and June 2010 were retrospectively reviewed. The retrospective review and the use of the clinical data followed the guidelines of the institutional ethics board of Kobe University Hospital, derived from the ethical guidelines for epidemiologic research by the Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labor and Welfare of Japan. The median age was 60 years (range, 22–85 years). There were 42 male (53.8%) and 36 female (46.2%) patients. A diagnosis of MALT lymphoma was established by biopsy or a surgical resection sample, and hemotoxylin and eosin–stained microscopic examination and immunohistochemical staining for CD20, CD3, CD5, and cyclinD1 were performed to exclude other pathologic subtypes.

Staging workup

Before starting the initial treatment, a physical examination, chest X-ray, complete blood count, MRI of both orbits, CT of the neck, chest, abdomen, and pelvis, and bone marrow biopsy were performed on all patients. Positron emission tomography, bone scan, or gallium scan was performed selectively. Tumors that were classified as stage IE in this study were unilateral or bilateral tumors without other lesions outside the orbit.

Treatment

Treatment policies differed according to treatment periods. From 1991 to 2004, a single modality of radiotherapy was used. From May 2000, a single modality of radiotherapy was mainly adopted, but a combination of radiotherapy and targeted therapy and/or chemotherapy was used in 3 patients. After 2004, a combination of radiotherapy and chemotherapy was used in 17 of 30 patients (56.7%). A total of 58 of the 78 patients (74.4%) were treated by radiotherapy alone, whereas the other 20 patients (25.6%) received targeted therapy or chemotherapy followed by radiotherapy. Among those treated with a combination of therapies, 17 patients had three or four courses of rituximab, 2 patients had two or three courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and 1 patient had an R-CHOP (rituximab and CHOP) regimen.

The radiation dose and schedule varied according to the treatment periods. Before February 2000, various radiation doses and schedules (range, 30–50 Gy in 18–25 fractions) were used in 17 patients. Since March 2000, a single schedule of 30.6 Gy in 17 fractions was adopted in the majority of patients (55 patients), with the exception of 3 patients who were treated with 32.4 Gy in 18 fractions (1 patient) or 36 Gy in 20 fractions (2 patients) (Table 1). In total, the median dose was 30.6 Gy. Forty-eight patients with disease at the conjunctiva, eyelid, and lacrimal gland were treated with electron beams (4–15 MeV) from a single anterior field. A cylindrical lead lens block, approximately 4 mm thick and 10 mm in diameter, was used with 4–15-MeV electron beams in 41 of the 48 patients (85.4%). The lens block was placed directly on the cornea after topical anesthesia. A 4-MeV photon beam was used in the other 30 patients (38.5%) for tumors located in the orbital soft tissue. Dose coverage and distribution of the tumor and surrounding critical structures were carefully considered with and without the use of a lens block, wedge, or bolus.

Follow-up evaluation and statistical analyses

In the follow-up evaluations, local and disease progression were evaluated every year using the same method as in the initial staging, with the exception of bone marrow biopsy. Morbidities were evaluated and re-graded by the ophthalmologist according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Local control, recurrence-free survival (RFS), overall survival (OS), and cause-specific survival (CSS) were analyzed statistically in all patients. Recurrence-free survival was calculated from the first day of radiotherapy to the date of first documented relapse or the date of death. Overall survival was calculated from the first day of radiotherapy to the date of death or the date of last follow-up. Curves for each survival type were calculated using Kaplan-Meier estimates. Statistical significance was tested by the log–rank test.

RESULTS

Tumor locations and characteristics

The tumor was located in the eyelid or conjunctiva in 37 patients (47.4%), the orbita in 29 patients (37.2%), and in the lacrimal gland in 12 patients (15.4%). Sixty-four patients

Table 1. Treatment methods in patients with POAML ($n = 78$)

Parameter	*n*	%
Initial treatment		
Radiotherapy alone	58	74.4
Targeted therapy and/or chemotherapy followed by radiotherapy	20	25.6
CHOP	2	2.6
Rituximab and CHOP	1	1.3
Rituximab	17	21.7
Radiation dose (median, 30.6 Gy)		
36–50 Gy/18–25 fractions	17	21.8
30–32.4 Gy/15–18 fractions	61	78.2
Radiation source		
6–12-MeV electron beam	48	61.5
4-MV photon beam	30	38.5

Abbreviations: POAML = primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone.

(82.1%) had unilateral lesions, and 14 patients (17.9%) had bilateral lesions.

Survival and causes of death

The median follow-up duration was 66 months (range, 3–234 months). Five-year and 10-year OS rates were 98.1% and 95.3%, respectively, and the 5- and 10-year CSS rates were both 100% (Fig. 1). None died of the disease; the deaths of 2 patients (2.6%) were from non–lymphoma-related causes.

LC, disease progression, and patterns of recurrence

There was no case that recurred locally, and therefore the 5- and 10-year LC rates were both 100% (Fig. 2). The 5- and 10-year RFS rates were 88.5% and 75.9%, respectively (Fig. 3). Patients treated with radiotherapy combined with targeted therapy and/or chemotherapy (5- and 10-year rates both 100%) showed a trend for better RFS than those who were treated with a single modality of radiotherapy (5- and 10-year rates: 85.3% and 71.1%, respectively; $p = 0.114$) (Fig. 4). Ten patients (12.8%) relapsed somewhere other than the original tumors (distant regions) (Table 2). The median duration to distant relapse was 33 months. Five patients (6.4%) relapsed at the contralateral orbit. Of the other 5 patients, 2 relapsed at nodes in the abdomen and the neck, 2 relapsed in the stomach, and 1 patient relapsed in the parenchyma of the lung. No patient showed the histology of a transformed high-grade lymphoma. Eight of the relapsed patients underwent a second-line therapy, and another 2 patients were observed without a second-line therapy (Table 2). One patient died from non–lymphoma-related causes. Notably, 20 patients (25.6%) treated with radiotherapy and targeted therapy and/or chemotherapy did not experience any distant or contralateral orbital recurrence (Table 3).

Morbidity

Any symptom related to the radiotherapy that occurred during from initial day to 1 month after completion of radiotherapy was defined as acute morbidity with reference to CTCAE version 3.0. Fifty-two patients (66.7%) had Grade 1 acute morbidity, and only 6 (7.7%) had Grade 2 acute morbidity. No patients developed greater than Grade 2 acute morbidity; the most frequent morbidities were mild conjunctivitis, excessive tearing or dryness, and periorbital erythema or edema.

There were 14 patients who experienced Grade 2 morbidities (cataract: 14; retinal disorders: 7; dry eye: 3), 23 patients who had Grade 3 morbidities (cataract: 23; dry eye: 1), and 1 patient who had Grade 4 glaucoma. Cataracts (Grade 3) were observed at a median 38 months (range, 9–88 months) after radiotherapy.

Risk factors for morbidity were retrospectively evaluated. For occurrence of retinal disorders (greater than Grade 2), the radiation dose was a significant risk factor (1.6% in patients treated with 30–32.4 Gy vs. 35.3% in patients treated with 36–40 Gy; $p < 0.0001$). Grade 2 retinopathies were observed in 5 patients, and a Grade 2 macular hole was observed in a patient who also developed a Grade 3 dry eye. Notably, these 6 patients received 36–40 Gy. The

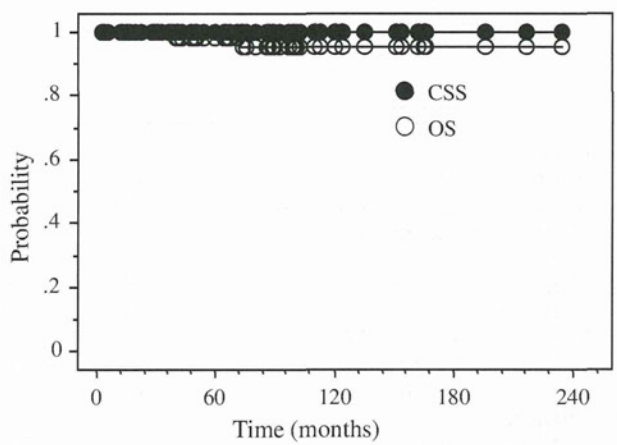

Fig. 1. Kaplan-Meier curves of cause-specific survival (CSS) and overall survival (OS) in patients with primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma ($n = 78$) (10-year CSS rate: 100%; 5- and 10-year OS rates: 98.1% and 95.3%, respectively).

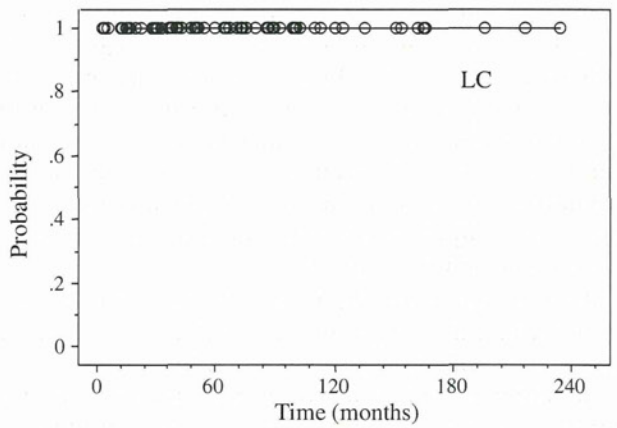

Fig. 2. Kaplan-Meier curve of local control (LC) in patients with primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma ($n = 78$) (10-year LC rate: 100%).

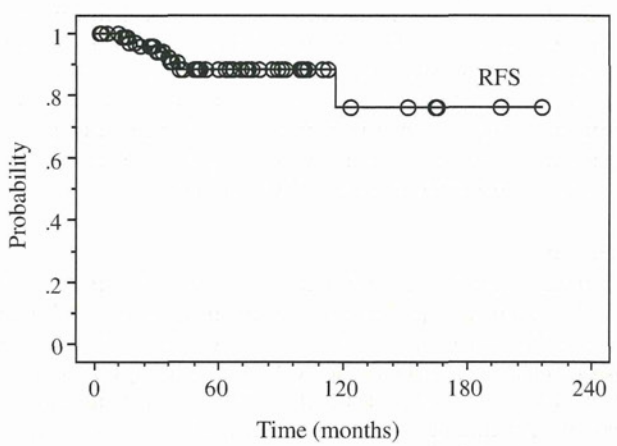

Fig. 3. Kaplan-Meier curve of recurrence-free survival (RFS) in patients with primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma ($n = 78$) (5- and 10-year RFS rates: 88.5% and 75.9%, respectively).

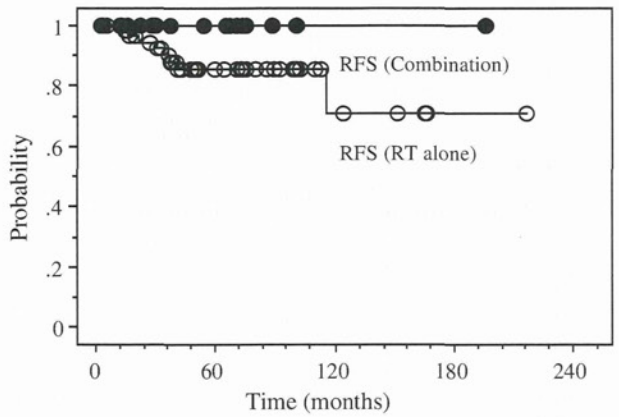

Fig. 4. Comparison of recurrence-free survival (RFS) in patients treated with a combination of targeted therapy and/or chemotherapy and radiotherapy (n = 20) and patients treated with radiation alone (n = 58) (10-year RFS rate of combination therapy: 100%, vs. 5- and 10-year RFS rates of radiotherapy alone: 85.3% and 71.1%, respectively).

other patient, who received 30.6 Gy, developed a retinal embolism (Grade 3). Grade 3 cataracts occurred in 13 of 61 patients (21.3%) treated with <36 Gy and in 10 of 17 patients (58.8%) treated with ≥36 Gy (p = 0.0027). A lens-sparing technique was used in 44 of the 78 patients (56.4%) whose tumor locations were conjunctiva or lacrimal gland. Nineteen of the 34 patients (55.9%) without lens shielding developed a Grade 3 cataract, whereas 4 of the 44 patients (9.1%) with lens shielding developed a cataract ($p < 0.001$). Although the lens-sparing technique was useful to avoid cataract, it was inadequate to use in case that tumor location was the orbita. Visual acuity of these 23 patients was successfully saved by cataract extraction. As a result, to avoid severe morbidities, a 30.6-Gy or lesser dose and the lens-sparing technique (restricted to the tumor at conjunctiva or lacrimal gland) might be recommended.

Prognostic factors

Several factors were evaluated for prognostic significance of RFS. Among them, combinations with targeted therapy and/or chemotherapy showed a trend for better RFS; however, it was not significant (with targeted therapy and/or chemotherapy [n = 20] vs. without targeted therapy and/or chemotherapy [n = 58], p = 0.114). Other factors, such as tumor location (conjunctiva [n = 37] vs. orbita [n = 29] vs. lacrimal gland [n = 12], p = 0.315), age (≤ 60 [n = 36] vs. > 61 [n = 42], p = 0.723), gender (male [n = 42] vs. female [n = 36], p = 0.201), and radiation dose (≤32.4 Gy [n = 61] vs. >36 Gy [n = 17], p = 0.575), were not significant.

DISCUSSION

The present study summarizes our institution's experience in a large cohort of POAML patients with long-term follow-up. Our study not only confirmed some of the previously reported observations but also elucidated patterns of failure and characteristics of Stage I POAML.

Excellent LC was achieved in our series of patients with Stage I POAML using moderate doses of 30 Gy. Previously, Fung *et al.* (26) reported that, in their series, the local relapse rate was higher in patients who received <30.6 Gy. Many authors have concluded that low-grade orbital lymphoma, including MALT, could be successfully controlled by radiation doses in the range of 25–34 Gy. Tsang and coworkers (13, 25) reported that, for LC, results from the use of a slightly lower dose of 25 Gy (in 10–15 fractions) in orbital lymphomas remained excellent. In our study, a median dose of 30.6 Gy was used, and 100% LC has been achieved. Therefore, the optimal radiation dose seems still to be a matter for discussion, and radiotherapy has remained the assumed standard for the initial treatment of POAML.

For localized MALT lymphoma, despite offering excellent LC, radiotherapy might not be useful in preventing systemic relapses, occurring in 5–45% of patients (8, 13, 18, 19, 22–31). Tsang *et al.* (13) demonstrated that although excellent LC can be achieved with infrequent long-term toxicity by a single modality of radiotherapy, the risk of relapse in distant extranodal sites remains a significant problem. Bayraktar *et al.* (31) demonstrated that patients with Stage I POAML face a continuous risk of distant relapse, which increases from an estimated cumulative progression rate of 17.8% at 5 years to 41.5% at 10 years. Therefore, the focus of POAML management may not only include LC but also

Table 2. Details of POAML patients who relapsed after radiotherapy

Patient	Age/ gender	Initial site	Radiation dose (Gy)	Relapse site	Duration to relapse (mo)	Treatment for relapse
1	40/F	Conjunctiva	30.6	Contralateral conjunctiva	13	Radiotherapy
2	73/M	Conjunctiva	36	Stomach	27	Endoscopic mucosal resection
3	49/F	Conjunctiva	30	Contralateral conjunctiva	116	Radiotherapy
4	63/F	Lacrimal gland	30.6	Contralateral conjunctiva	21	Rituximab and chemotherapy and radiotherapy
5	49/M	Lacrimal gland	40	Lymph nodes	30	Rituximab and chemotherapy
6	40/F	Lacrimal gland	30	Stomach	41	Radiotherapy
7	77/M	Orbit	36	Lymph nodes and spleen	17	Rituximab and chemotherapy
8	54/M	Orbit	40	Contralateral orbit	36	Rituximab and chemotherapy
9	72/F	Orbit	30.6	Contralateral orbit	37	No treatment (observation)
10	50/F	Orbit	40	Lung parenchyma	86	No treatment (observation)

Abbreviations: F = female; M = male. Other abbreviation as in Table 1.

Table 3. Patterns of relapses in patients with stage I-II POAML treated with radiotherapy

First author (reference)*	Reported year	*N*	Clinical stage (I/II/III/IV)	Median follow-up (mo)	Radiation dose (Gy)	No. of patients			
							Sites of relapsed tumors		
						Total	Local	Contralateral orbit	Distant
Tsang (13)	2003	30	I-II:30/0/0	60	25	8	2	3	3
Uno (18)	2003	50	50/0/0/0	46	36	6	3	0	3
Suh (32)	2006	48	46/1/0/1	70	30.6	3	3	0	0
Ejima (23)	2006	42	42/0/0/0	48	30.6	8	0	4	4
Nam (27)	2009	66	66/0/0/0	50	30	6	3	2	3
Goda (25)	2010	71	I-II:71/0/0	89	25	18	3	5	11†
Son (28)	2010	46	46/0/0/0	32	30.6	2	0	1	1
Bayraktar (31)	2011	70	70/0/0/0	60	30.6	14	6	NA	10
Total		423				65 (15.4)	20 (4.7)	15 (3.5)	35 (8.3)
Present study	2011	58	58/0/0/0	73.5	RT: 30.6	10 (17.2)	0	5 (8.6)	5 (8.6)
		20	20/0/0/0	45.5	RT: 30.6 + rituximab	0	0	0	0
Total	2011	78	78/0/0/0	66		(12.8)	0	(6.4)	(6.4)

Abbreviation: RT = radiotherapy. Other abbreviation as in Table 1.
Values in parentheses are percentages.
* The listed articles all included outcome of RT for Stage I–II POAML. Other articles contained various histologic orbital tumors, or articles included more than 10% stage III–IV MALT disease were not included.
† Extraorbital recurrence.

systemic disease control. However, the significance of chemotherapy for systemic disease control has not been widely accepted in the initial treatment of MALT lymphoma. A large, retrospective study conducted by the International Extra Nodal Lymphoma Study Group analyzed the results of 180 patients, including patients with Stage I–IV MALT lymphoma, and did not find any difference in the clinical outcome between initial localized treatment approaches with systemic chemotherapy (29). The efficacy of the combination of radiotherapy and chemotherapy has not been fully investigated. Goda *et al.* (25) reported that the initial role of chemotherapy could not be determined in their series; however, they suggested that it must have contributed to control of the disease because all patients had partial or complete responses from chemotherapy before the initiation of radiotherapy. We searched for all articles published between 2000 and 2011 that included the outcome in patients with Stage I–II POAML (Table 3); previous investigators reported similar risks of local relapse, contralateral relapse, and distant relapses when patients were treated with radiation alone (12, 17, 22, 24, 26, 27, 32). In our series, although the cohort who received radiotherapy alone had similar pattern of relapse, notably, the outcome of the other cohort treated with combined radiotherapy and rituximab showed decreased systemic relapse (Table 3).

The best way to treat POAML should be considered carefully to avoid overtreatment. A combination of reduced-dose radiotherapy and rituximab could be proposed as an optimal treatment for POAML. Several examples in the treatment of lymphoma or medulloblastoma using a strategy of reduced radiation doses with chemotherapy have been investigated (33–36). Conversely, there are few data regarding how much the dose could be reduced safely in the combination. In our series, the protocol consisting of 30.6 Gy radiotherapy combined with rituximab successfully decreased risks of systemic relapse. However, it remains unknown whether doses less than 30.6 Gy might keep satisfying LC and whether those doses lead to reduced risks of morbidity, including cataract. Therefore, future clinical trials seem to be necessary to set optimal doses in the strategy of combination therapy.

In conclusion, radiotherapy for POAML was highly effective and safe for LC and OS. The absence of systemic relapse in patients with combined-modality treatment suggests that lower doses of radiation combined with targeted therapy may be worth further study.

REFERENCES

1. Isaacson PG, Wright D. Malignant lymphoma of mucosa-associated lymphoid tissue: A distinctive type of B-cell lymphoma. *Cancer* 1983;52:1410–1416.
2. Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasm: A proposal from the International Lymphoma Study Group. *Blood* 1994; 84:1361–1392.
3. Isaacson PG, Muller-Hermelink HK, Piris MA, *et al.* Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Jaffe ES, Harris NI, Stein H, *et al.*, editors. World Health Organization classification of tumors. Pathology genetics of haematopoietic and lymphoid tissue. Lyon, France: IARC Press; 2001. pp. 157–160.

4. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972;29:252–260.
5. White WL, Ferry JA, Harris NL, *et al.* Ocular adnexal lymphoma: A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. *Ophthalmology* 1995;102:1994–2006.
6. Nakata M, Matsuno Y, Katsumata N, *et al.* Histology according to the revised European-American Lymphoma classification significantly predicts the prognosis of ocular adnexal lymphoma. *Leuk Lymphoma* 1999;32:533–543.
7. Cho EY, Han JJ, Ree HJ, *et al.* Clinicopathologic analysis of ocular adnexal lymphomas: Extranodal marginal zone B-cell lymphoma constitutes the vast majority of ocular lymphomas among Koreans and affects younger patients. *Am J Hematol* 2003;73:87–96.
8. Jenkins C, Rose GE, Bunce C, *et al.* Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival. *Br J Ophthalmol* 2000;84:907–913.
9. Auw-Haedrich C, Coupland SE, Kapp A, *et al.* Long term outcome of ocular adnexal lymphoma subtyped according to the REAL classification. *Br J Ophthalmol* 2001;85:63–69.
10. Thieblemont C, Bastion Y, Berger F, *et al.* Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior. *J Clin Oncol* 1997;15:1624–1630.
11. Thieblemont C, Berger F, Dumontet C, *et al.* Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000;95:802–806.
12. Song EK, Kim SY, Kim TM, *et al.* Efficacy of chemotherapy as a first-line treatment in ocular adnexal extranodal marginal zone B-cell lymphoma. *Ann Oncol* 2008;19:242–246.
13. Tsang RW, Gospodarowicz MK, Pintilie M, *et al.* Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003;21:4157–4164.
14. Tsang RW, Gospodarowicz MK, Pintilie M, *et al.* Stage I and II MALT lymphoma: Results of treatment with radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;50:1258–1264.
15. Le QT, Eulau SM, George TI, *et al.* Primary radiotherapy for localized orbital MALT lymphoma. *Int J Radiat Oncol Biol Phys* 2002;52:657–663.
16. Bhatia S, Paulino AC, Buatti JM, *et al.* Curative radiotherapy for primary orbital lymphoma. *Int J Radiat Oncol Biol Phys* 2002;54:818–823.
17. Martinet S, Ozsahin M, Belkacemi Y, *et al.* Outcome and prognostic factors in orbital lymphoma: A rare cancer network study on 90 consecutive patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;55:892–898.
18. Uno T, Isobe K, Shikama N, *et al.* Radiotherapy for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa. *Cancer* 2003;98:865–871.
19. Tanimoto K, Kaneko A, Suzuki S, *et al.* Primary ocular adnexal MALT lymphoma: A long-term follow-up study of 114 patients. *Jpn J Clin Oncol* 2007;37:337–344.
20. Lee JL, Kim MK, Lee KH, *et al.* Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue type of the orbit and ocular adnexa. *Ann Hematol* 2005;84:13–18.
21. Charlotte F, Doghmi K, Cassoux N, *et al.* Ocular adnexal marginal zone B cell lymphoma: A clinical and pathologic study of 23 cases. *Virchows Arch* 2005;2:1–11.
22. Raderer M, Streubel B, Woehrer S, *et al.* High relapse rate in patients with MALT lymphoma warrants lifelong follow-up. *Clin Cancer Res* 2005;11:3349–3352.
23. Ejima Y, Sasaki R, Okamoto Y, *et al.* Ocular adnexal mucosa associated lymphoid tissue lymphoma treated with radiotherapy. *Radiother Oncol* 2006;78:6–9.
24. Fung CY, Tarbell NJ, Lucarelli MJ, *et al.* Ocular adnexal lymphoma: Clinical behavior of distinct world health organization classification subtypes. *Int J Radiat Oncol Biol Phys* 2003;57:1382–1391.
25. Goda JS, Gospodarowicz M, Pintilie M, *et al.* Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. *Cancer* 2010;116:3815–3824.
26. Hasegawa M, Kojima M, Shioya M, *et al.* Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. *Int J Radiat Oncol Biol Phys* 2003;57:172–176.
27. Nam H, Ahn YC, Kim YD, *et al.* Prognostic significance of anatomic subsites: Results of radiation therapy for 66 patients with localized orbital marginal zone B cell lymphoma. *Radiother Oncol* 2009;90:236–241.
28. Son SH, Choi BO, Kim GW, *et al.* Primary radiation therapy in patients with localized orbital marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT Lymphoma). *Int J Radiat Oncol Biol Phys* 2010;77:86–91.
29. Zucca E, Conconi A, Pedrinis E, *et al.* Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003;101:2489–2495.
30. Wenzel C, Fiebiger W, Dieckmann K, *et al.* Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue of the Head and Neck Area. *Cancer* 2003;97:2236–2241.
31. Bayraktar S, Bayraktar UD, Stefanovic A, *et al.* Primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (MALT): Single institution experience in a large cohort of patients. *Br J Haematol* 2011;152:72–80.
32. Suh CO, Shim SJ, Lee SW, *et al.* Orbital marginal zone B-cell lymphoma of MALT: Radiotherapy results and clinical behavior. *Int J Radiat Oncol Biol Phys* 2006;65:228–233.
33. Engert A, Plütschow A, Eich HT, *et al.* Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640–652.
34. Shah GD, Yahalom J, Correa DD, *et al.* Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2007;25:4730–4735.
35. Oyharcabal-Bourden V, Kalifa C, Gentet JC, *et al.* Standard-risk medulloblastoma treated by adjuvant chemotherapy followed by reduced-dose craniospinal radiation therapy: A French Society of Pediatric Oncology Study. *J Clin Oncol* 2005;23:4726–4734.
36. Merchant TE, Kun LE, Krasin MJ, *et al.* Multi-institution prospective trial of reduced-dose craniospinal irradiation (23.4 Gy) followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy) and dose-intensive chemotherapy for average-risk medulloblastoma. *Int J Radiat Oncol Biol Phys* 2008;70:782–787.

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 626–634, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.11.037

CLINICAL INVESTIGATION **Lymphoma**

MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY

Ryohei Sasaki, M.D.,* Koichi Yasuda, M.D.,† Eisuke Abe, M.D.,‡ Nobue Uchida, M.D.,§ Mitsuhiko Kawashima, M.D.,‖ Takashi Uno, M.D.,¶ Masayuki Fujiwara, M.D.,# Yoshiyuki Shioyama, M.D.,** Yoshikazu Kagami, M.D.,†† Yuta Shibamoto, M.D.,‡‡ Kensei Nakata, M.D.,§§ Yoshie Takada, M.D.,‖‖ Tetsuya Kawabe, M.D.,* Kazuyuki Uehara, M.S.,* Kenichi Nibu, M.D.,¶¶ and Syogo Yamada, M.D.##

*Division of Radiation Oncology, ¶¶Division of Otolaryngology–Head and Neck Surgery, Kobe University Graduate School of Medicine, †Department of Radiology, Hokkaido University School of Medicine, ‡Division of Radiation Oncology, Graduate School of Medical and Dental Sciences, Niigata University, §Department of Radiation Oncology, Shimane University Faculty of Medicine, ‖Radiation Oncology Division, National Cancer Center Hospital East, ¶Department of Radiology, Graduate School of Medicine, Chiba University, #Department of Radiology, Hyogo College of Medicine, **Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, ††Radiation Oncology Division, National Cancer Center Hospital, ‡‡Department of Radiology, Nagoya City University Graduate School of Medical Sciences, §§Department of Radiology, Sapporo Medical University, ‖‖Department of Radiology, Osaka City University Graduate School of Medicine, ##Department of Radiation Oncology, Tohoku University School of Medicine

Purpose: The purpose of this study was to elucidate the efficacy and optimal method of radiotherapy in the management of solitary extramedullary plasmacytoma occurring in the head and neck regions (EMPHN).
Methods and Materials: Sixty-seven patients (43 male and 24 female) diagnosed with EMPHN between 1983 and 2008 at 23 Japanese institutions were reviewed. The median patient age was 64 years (range, 12–83). The median dose administered was 50 Gy (range, 30–64 Gy). Survival data were calculated by the Kaplan-Meier method.
Results: The median follow-up duration was 63 months. Major tumor sites were nasal or paranasal cavities in 36 (54%) patients, oropharynx or nasopharynx in 16 (23%) patients, orbita in 6 (9%) patients, and larynx in 3 (5%) patients. The 5- and 10-year local control rates were 95% and 87%, whereas the 5- and 10-year disease-free survival rates were 56% and 54%, respectively. There were 5 (7.5%), 12 (18%), and 8 (12%) patients who experienced local failure, distant metastasis, and progression to multiple myeloma, respectively. In total, 18 patients died, including 10 (15%) patients who died due to complications from EMPHN. The 5- and 10-year overall survival (OS) rates were 73% and 56%, respectively. Radiotherapy combined with surgery was identified as the lone significant prognostic factor for OS ($p = 0.04$), whereas age, gender, radiation dose, tumor size, and chemotherapy were not predictive. No patient experienced any severe acute morbidity.
Conclusions: Radiotherapy was quite effective and safe for patients with EMPHN. Radiotherapy combined with surgery produced a better outcome according to survival rates. These findings require confirmation by further studies with larger numbers of patients with EMPHN. © 2012 Elsevier Inc.

Extramedullary plasmacytoma, Radiotherapy, Head and neck, Multi-institutional analysis.

INTRODUCTION

Plasma cell malignancies include multiple myeloma (MM), solitary plasmacytoma of the bone (SPB), and extramedullary plasmacytoma (EMP). EMP is a rare tumor representing approximately 3% of all plasma cell tumors, yielding an MM:SPB:EMP incidence ratio of approximately 40:2:1 (1–4). The incidence of EMP has been measured at 0.04 cases per 100,000 individuals (5). Although EMP can arise throughout the body, almost 90% of tumors arise in the head and neck, especially in the upper respiratory tract, including the nasal cavity, sinuses, oropharynx, salivary

Reprint requests to: Ryohei Sasaki, M.D., Ph.D., Division of Radiation Oncology, Kobe University Graduate School of Medicine, 7-5-2 Kusunokicho, Chuouku, Kobe City, Hyogo, 650-0017, Japan. Tel: +81-78-3826104; Fax: +81-78-3826129; E-mail: rsasaki@med.kobe-u.ac.jp

Parts of this study were presented at the 51th Annual meeting of ASTRO, Chicago, IL, November 1–5, 2009.

Conflict of interest: none.

Acknowledgment—Grants-in-aid 18209040 and 21249066 (S.Y., R.S.) for Scientific Research, Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Received Aug 19, 2010, and in revised form Nov 6, 2010. Accepted for publication Nov 9, 2010.

glands, and larynx (4, 6–10). The next most frequent site of occurrence is the gastrointestinal tract. A variety of other sites, including testis, bladder, urethra, breast, ovary, lung, pleura, thyroid, orbit, brain, and skin, can be involved, albeit infrequently (11–21). Patients typically present in the fifth to seventh decade of life with localized submucosal masses or swellings and symptoms related to compression and obstruction of local structures.

Solitary extramedullary (soft-tissue) plasmacytoma is less common than SPB but carries a better prognosis, because the majority of patients can be cured by local radiotherapy (22). The optimal management of EMP of the head and neck (EMPHN) is a matter of debate. Radiotherapy plays a central role in the treatment of EMP, even though the optimal radiationdose and the role of elective irradiation of regional lymphatics are still undetermined (23). Surgery can also be considered as an alternative first-line therapy (6). Surgery can achieve high rates of local control in certain situations. However, radical excision is often impossible because of the size of the tumor, the proximity of critical normal structures and the risk of poor cosmetic results. Potential morbidity associated with surgery and the radiosensitivity of EMP have made radiotherapy the mainstay of treatment at most centers (7, 24). On the contrary, the role of chemotherapy in the treatment of primary tumors or recurrent disease or in preventing or delaying progression to MM remains controversial (3, 25, 26). Adjuvant chemotherapy has not been shown to reduce relapse rates or to improve survival rates and, at present, has no place in the primary management of EMP (24, 27, 28). Therefore, close communication among radiation oncologists, surgeons, and hematological oncologists is crucial for the optimum care for this disease.

The purpose of this study was to elucidate the efficacy and the optimal method of radiotherapy in the management of EMPHN.

Table 1. Patients and tumor characteristics

	Number	Percentage (%)
Age	12–83 (64)*	
Gender (M/F)	43/24	
ECOG performance status (0/1/2/unknown)	46/18/1/2	
Tumor size	1–10 cm (3.5)*	
Sites		
Nasal/paranasal	36	54
Oropharynx	9	13
Nasopharynx	7	10
Orbita	6	9
Larynx	3	5
Salivary glands	2	3
Lymph nodes	2	3
Middle ear	1	1.5
Thyroid	1	1.5
Positive for M protein	15/59	22
Positive for Bence-Jones proteins	2/56	4
Concomitant disease		
Amyloidosis	2/67	3

* median age, median tumor size.

PATIENTS AND METHODS

Medical records of all patients treated for EMPHN at 23 institutions in Japan between 1983 and 2008 were retrospectively reviewed. Patients were identified from databases at each institution. This study was approved by the Kobe University Hospital and each relevant institutional Review Board. Patients were considered eligible for inclusion if they had a single lesion in the head or neck and a diagnosis of EMP based on a biopsy showing features characteristic of plasmacytoma, a negative skeletal survey, and a normal bone marrow biopsy. Patients with evidence of myeloma at the time of presentation were excluded. Then, a total of consecutive 67 patients from the 23 institutions were investigated. In general, patients were seen at follow-up evaluations every 3 months for the first 2 years, every 6 months for an additional 3 years, and then yearly or every other year thereafter. Follow-up imaging included fiberoptic endoscopy

Table 2. Details of treatments

	Total numbers of patients (%)	Age <50	Age ≥50	*p* value
Treatment policy				
Without surgery*	44 (66)	10	34	0.93*
Radiotherapy alone	39 (58)	8	31	
Radiotherapy combined with chemotherapy	5 (8)	2	3	
With surgery*	23 (34)	5	18	
Surgery followed by radiotherapy	19 (28)	4	15	
Radiotherapy followed by surgery with or without chemotherapy	4 (6)	1	3	
Radiation dose (BED: median, minimum, and maximum)				
Median: 50 Gy, 1.8–2 Gy per fraction				
≤40 Gy (BED: 46.7, 36, and 48)	13 (20)	4	9	0.41
40.1–45 Gy (BED: 51, 50.4, and 53)	4 (6)	1	3	
45.1–50 Gy (BED: 60, 55.2, and 60)	39 (58)	6	33	
50.1–64 Gy (BED: 72, 59.5, and 76.8)	11 (16)	4	7	
Radiation fields				
Primary sites	51 (76)	11	40	0.2
Primary sites and regional nodes	16 (24)	6	10	

Abbreviation: BED = biologically effective dose.
$\alpha/\beta = 10$.
*Subgroups treated radiotherapy without surgery ($n = 44$) or with surgery ($n = 23$) were evaluated by a chi-square test.

Table 3. Relationship of tumor size and radiation dose in patients treated with radiotherapy and without surgery

Radiation dose	Total numbers of patients (%)	Tumor size ≤5 cm	Tumor size >5 cm	*p* value
Without surgery ($n = 42$*)				
≤45 Gy	10	8	2	0.75
>45.1 Gy	32	27	5	
With surgery ($n = 16$†)				
≤45 Gy	5	4	1	0.33
>45.1 Gy	11	6	5	

*Two cases were excluded because their tumor sizes were not identified exactly.

†Seven cases were excluded with the same reason.

at each visit and computed tomography and/or magnetic resonance imaging every 6–12 months.

Statistical analysis

Statistical analysis was performed using Statview software (SAS Institute, Cary, NC) . Time to event was calculated from the starting

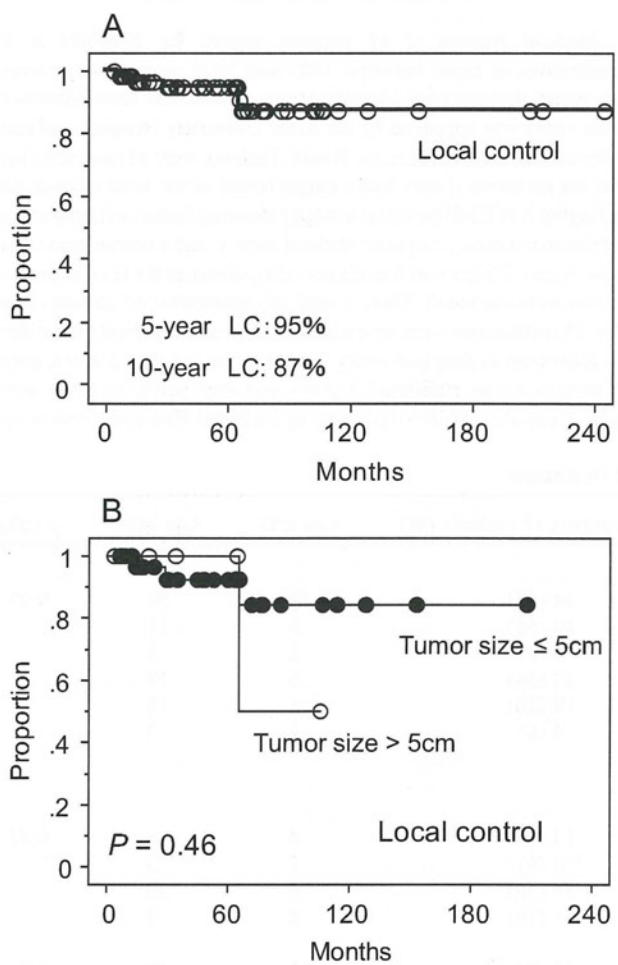

Fig. 1. (A) Local control rate for extramedullary plasmacytoma of the head and neck (EMPHN) ($n = 67$). (B) Comparison of local control rate according to the tumor size in patients treated with radiotherapy and without surgery ($n = 42$). Log–rank test was used for evaluation.

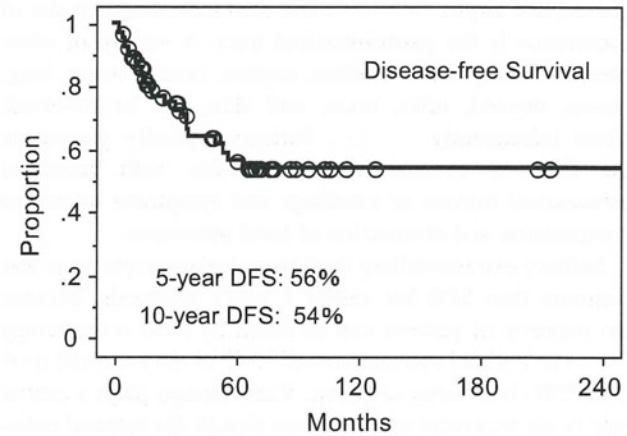

Fig. 2. Disease-free survival rate for extramedullary plasmacytoma of the head and neck (EMPHN) ($n = 67$).

date of radiotherapy to the event of interest, which was death (from any cause) for overall survival, first failure (death or disease) for disease-free survival (DFS), and local recurrence as confirmed by biopsy for recurrence rates. The Kaplan-Meier method was used to calculate the survival and recurrence curves. Follow-up duration was estimated for surviving patients. Differences in local recurrence rates between factors were calculated using the log–rank test.

RESULTS

Patients and treatments

Details of tumor characteristics are shown in Table 1. The median age at diagnosis was 64 years, with a range of 12–83 years. In this study, 43 patients were male, and 24 patients were female. The median tumor size was 3.5 cm (range, 1–10 cm). The most frequent tumor sites were nasal or paranasal cavities. Proportions of patients with positive M protein, Bence-Jones protein, and concomitant disease are listed in Table 1. External beam radiation therapy was used in all cases. A 4- to 10-megavolt photon beam was primarily applied for 57 patients, whereas a telecobalt gamma ray was used for 8 patients. Electron beam irradiation was used for 2 patients. The radiation dose ranged from 30 to 60 Gy, with a median dose of 50 Gy. Treatment policies, radiation dose, and radiation fields are listed in the Table 2. Although all patients were treated with 1.8–2 Gy per fraction, total doses were ranging from 30 to 64 Gy, and biological effective doses (BED) were ranging from 36 to 76.8 Gy calculated by using a ration of $\alpha/\beta = 10$ (Table 2). The treatment methods, choice of total dose, and choice of irradiation for regional lymph nodes were depending on each physician's decision. Treatment choice was not differ significantly according to the age (<50 or ≥50) (Table 2). Radiation dose did not differ significantly as a function of tumor size in a subgroup without surgery ($p = 0.75$) and in a subgroup with surgery ($p = 0.33$) (Table 3).

Local control

The median follow-up duration was 63 months. Local recurrences developed in 7.5% of patients (5 of 67). The mean